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Emergent/Urgent Therapeutic Irradiation in Pediatric Oncology: Patterns of Presentation, Treatment, and Outcome

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Purpose. We reviewed all pediatric cases referred for emergent/urgent therapy (requiring treatment within 48 hours) to identify frequency, patterns of presentation, and efficacy of therapy. We defined five categories of emergent/urgent therapy based on irradiated site and/or signs: Group I, spinal cord compression; Group II, respiratory compromise; Group III, infradiaphagmatic distress; Group IV, intracranial signs; Group V, pain.

Materials and Methods. From 2/1/88–3/1/94, 104 children with 115 problems were referred by specialists at the Children's Hospital of Philadelphia. Diagnosis, nature of the emergency, and response were examined. Responses were categorized as complete resolution, improvement or stabilization, and progression.

Results. The 104 children represented 12% of referrals during the study period. The most common tumors were CNS PNET and gliomas (20%); and neuroblastoma (20%). Forty-five problems occurred with newly diagnosed tumors and 70 after progression. Ninety-one episodes were managed with radiation therapy and 24 with other modalities.

Patients with spinal cord/cauda equina (n = 33) compression improved (55%) or stabilized (30%). Patients with respiratory compromise from thoracic (n = 14) or abdominal (n = 5) disease had a response rate of 72%. Eight patients in group III had a 66% response. In Group IV (n = 16), 63% had complete responses and 19% had stabilization. Group V (n = 15) patients had a complete or partial response of 93%.

Conclusion. Approximately 10% of children referred for radiation therapy required emergent/urgent treatment. Eighty percent of patients achieved stabilization or showed improvement in signs and symptoms, indicating that radiotherapy is a valuable and reliable component of multimodal care in such situations. Med. Pediatr. Oncol. 30:101–105, 1998.

Key words: oncologic emergency; pediatric oncology; radiation therapy; superior vena cava syndrome; superior mediastinal syndrome; spinal cord compression

INTRODUCTION

Much of the radiotherapy literature focusing on emergency therapy involves adults treated for spinal cord compression [1–3] or the superior vena cava syndrome [4,5]. There have been no reported systematic studies concerning oncologic emergencies in children that were managed by radiation therapy (RT). The diseases responsible for these syndromes differ between adult and children, as does their clinical evolution [6]. Oncologic emergencies generally presented earlier in the course of the disease in children, may often be the presenting symptom [7–9], and do not necessarily carry the grim prognosis that characterizes adult emergencies [2,4,8–11]. In addition, cancers in children tend to be more chemosensitive and radiosensitive than those in adults. In our institution, refractory pain is considered an indication for urgent palliative RT in children, compared with the usual management in adults, in whom pain management with narcotics is foremost and palliative RT is delivered within a more routine time frame.

This report retrospectively analyzes all patients referred to a radiation oncology department for radiotherapy over a 6-year period for management of medical complications considered to be emergent or urgent. We identified the frequency and patterns of presentation of these oncologic emergencies and evaluated the efficacy of radiotherapy in the combined modality management of such situations.

MATERIALS AND METHODS

Between February 1, 1988, and March 1, 1994, 884 pediatric patients were referred from the Children's Hos-

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pital of Philadelphia to the Department of Radiation Oncology of the Hospital of the University of Pennsylvania. One hundred fifteen patients had emergent/urgent problems requiring treatment within 48 hours. Among the 115 was one child with two synchronous urgent problems, each of which is considered separately. Irradiation was a component of a combined modality treatment plan in 91 of the 115 (79%) of episodes referred. Reasons for not receiving RT in the remaining 24 were chemotherapy or surgery selected instead (15), previous radiation therapy (3), family refusal (2), young age (2), rapid deterioration (1), spontaneous tumor regression (1). Chemotherapy was administered concurrently or shortly following radiation in 80 of 90 cases (one unknown).

We categorized the 91 treated problems into 5 groups based on the locus irradiated and/or signs at presentation. Group I includes 33 patients who were treated for spinal cord compression with either neurologic symptoms or pain. The most common symptoms were weakness or paralysis (n = 20) and severe pain (n = 13). Four patients had bladder/bowel dysfunction. Group II consists of 18 patients with respiratory difficulties from thoracic disease (n = 14) or large abdominal tumors causing respiratory compromise (n = 5). One patient received treatment for both an abdominal and a thoracic mass. Group III comprises 8 patients who received abdominal treatment for a variety of reasons: renal dysfunction from leukemia (1), inferior vena caval compression from hepatomegaly (1), gastrointestinal obstruction (3), splenomegaly (1), pain from peritoneal seeding (1), and ureteral obstruction (1). Group IV includes 16 patients with intracranial problems who were treated for neurologic compromise. The most common symptoms were cranial nerve palsies (n = 10) and respiratory failure/obtundation (n = 5). Group V consists of 15 patients treated only for palliation of severe or refractory pain within 48 hours of presentation. The most common causes of pain were bone metastases (n = 10) and large neck lymph nodes (n = 4). One patient with a hemangioma of the neck treated for thrombocytopenia due to a large mass is included in the refractory pain subgroup because she also had pain.

The indications for emergent/urgent treatment varied from, at one end, life-threatening emergencies (i.e., acute respiratory distress from mediastinal disease or airway obstruction, respiratory failure from brain stem tumor) to organ-threatening emergencies that were not immediately life threatening. They nonetheless were thought to jeopardize the integrity or function of a critical organ (e.g., the spinal cord) with a high potential for morbidity. At the other end were children with tumors that threatened less serious consequences or that affected the child's sense of well being (i.e., cranial nerve deficits causing diplopia, severe refractory bone pain from metastases).

Radiotherapy fields, fractionation, and doses were individualized based on each presenting symptom, the underlying diagnosis, the age of the child, and the prognosis. Consequently, techniques and doses varied considerably. In general, solid tumors were treated with fraction sizes of 1.5–4.0 Gy to total doses ranging from 3.0–55.8 Gy. Smaller total doses in the range of 2.2–22.5 Gy were utilized for lymphomas and leukemia. Efficacy of radiotherapy was measured by symptomatic response in the judgment of the treating physician(s). Response was graded as complete resolution of presenting symptoms, improvement, stabilization, no response, or progression.

RESULTS

The 104 children represent 12% of the 884 pediatric patients referred to our institution during the 6-year study period. The group was composed of 65 males and 39 females ranging in age from newborn to 21 years (median age 8.0 years). In 45 of the 115 problems among the 104 patients, the cause for immediate referral was the symptom or sign that led to the diagnosis of cancer, while the remainder (n = 71) were the result of relapses of previously known disease. Radiation therapy was used alone or with other modalities in managing 91 of the 115 emergency episodes (79%). Reasons for excluding the other 24 are given above. The median age of the 91 treated patients was 7.9 years and 8.1 years for those not treated with radiation.

A wide spectrum of tumors was responsible for the various symptoms (Table I); the most common were of neural origin. Central nervous system primitive neuroectodermal tumors (PNET) (n = 15), gliomas (n = 6), and astrocytomas (n = 4) accounted for 20% of the 115 referrals. Neuroblastoma (n = 24) accounted for another 20%. Group I patients (n = 33) primarily presented with spinal cord/cauda equina compression or intrinsic cord lesions. Spinal cord compression was caused mainly by ''drop'' metastases from intracranial tumors (n = 14) or by extradural compression caused by sarcomas (n = 10). Eighty-five percent of the 33 patients experienced improvement (55%) or stabilization (30%) of neurologic signs. Two children had no response and 3 had progression of disease.

Among the 18 patients in Group II, respiratory compromise was most frequently a result of the superior mediastinal syndrome (SMS) (n = 12). A massive intra-abdominal mass causing inadequate diaphragmatic excursion or inferior vena caval compression was the cause of respiratory distress in 5 patients. There was a 72% response rate in this group.

Group III was the most heterogeneous of the treatment groups: these patients, with abdominal difficulties, had multiple diagnoses and reasons for treatment. The 8 patients in Group III had a 66% response rate.

TABLE I. Tumors Responsible for Symptoms in Study Group

Group number	Group name	Pathology	Symptoms
I (n = 33)	Spinal cord compression	PNET (10), Ewings (4), rhabdomyosarcoma (3), leukemia (3), lymphoma (2), Wilms (2), astrocytoma (2), MFH (1), LCH (1), fibrosarcoma (1), neuroblastoma (1), ependymoma (1), osteogenic sarcoma (2)	Pain (13), bowel/bladder (4), paresthesia (5), weakness (20)
II (n = 8)[a]	Thoracic	Neuroblastoma (6), Wilms (4), NHL (3), ALL (1), Ewings (1), rhabdomyosarcoma (1), endodermal sinus tumor (1), hemangioma (1)	Mediastinal/airway (14), abdominal (5)
III (n = 8)	Abdominal	Neuroblastoma (5), ALL (2),nasopharynx (1)	GI obstruction (3), splenomegaly (1), IVC compression (1), renal dysfunction (1), ureteral obstruction (1), peritoneal seeding (1)
IV (n = 16)	Intracranial	Glioma (6), PNET (4), leukemia (2), craniopharyngioma (1), germinoma (1), nasopharynx (1), neuroblastoma (1)	Cranial nerve palsies (7), respiratory failure (5), cyst reacculumation (2), nausea/vomiting (2)
V (n = 15)	Pain	Neuroblastoma (7) sarcoma (3), hemangioma (1), nasopharynx (1), retinoblastoma (1), leukemia (1), lymphoma (1)	Bone metastasis (10), neck mass (4), soft tissue (1)

[a]One patient with disease in both abdominal and thoracic regions was treated in both sites.

Group IV patients, who had intracranial tumors (n = 16), had a 63% response to treatment and 19% had stable disease. Six had cranial nerve deficits, 5 experienced decreased respiratory function/obtundation, and 2 were treated to prevent CSF reaccumulation after shunt placement. Two others had intractable nausea and vomiting due to cerebellar masses, and 1 was treated urgently for a skull mass invading the brain.

Group V patients (n = 15) had refractory pain—10 because of bone metastases, 4 from neck masses (enlarged lymph nodes), and 1 from a soft tissue mass. There was a 93% response rate (complete and partial) in this group of patients.

DISCUSSION

Childhood cancer is uncommon: each year, only 1 in about 10,000 children develops a malignant disease. Some of these diagnoses are first made when the patients present with problems requiring urgent or emergency treatment, but such therapy may be needed at any time during the course of the illness. Little has been reported regarding the frequency or the types of problems requiring urgent RT consultation for children with cancer.

This report is the first comprehensive description of the patterns of presentation and results of radiotherapy in the multimodal management of pediatric oncologic emergencies. It is based on a large number of children with cancer (884) referred to the Department of Radiation Oncology of the Hospital of University of Pennsylvania from the Children's Hospital of Pennsylvania during a 6-year period. There were 115 emergent/urgent referrals during this interval, representing 104 children and 116 problems. Eighty of the 90 cases treated with radiation also received chemotherapy, either concurrently or shortly afterwards. It is difficult to assess the benefits of radiation alone in this setting, the responses seen can be attributed to the combined effects of radiation and chemotherapy, but early RT intervention was considered necessary because there was not time to await the uncertain efficacy of alternate therapies.

Spinal cord compression is considered an emergency because of the threat of permanent paralysis. Four percent of children with cancer will develop spinal cord compromise [12]. Four mechanisms are responsible: 1) direct spread of the tumor, 2) metastatic vertebral bone disease with secondary cord compression, 3) spread to the epidural space by infiltration through the intervertebral foramina [13], and 4) drop metastases from an intracranial tumor. Although the signs of spinal cord compression in children are similar to those in adults, the etiology, prognosis, and response to treatment can be very different. In adults, spinal cord compression is most often caused by lung, breast, and prostate tumors [6,14], whereas in children, sarcomas account for 43% to 65% of cases [7,9]. Neuroblastoma is reportedly the second most common etiology [7,9], but brain tumors (14 of 33 [42%]) and sarcomas (10 or 33 [30%]) accounted for most of our cases. Adults who are non-ambulatory at presentation rarely regain function [1,3], whereas more than 50% of paraplegic children become ambulatory with appropriate therapy [10,12,15].

Signs and symptoms most commonly associated with spinal cord compression are motor weakness in 67% of patients; pain in 50%; and sensory disturbances, including bowel and bladder dysfunction, in 30% [16]. In our

series, 70% of patients presented with weakness, 40% with pain, 12% with bowel/bladder dysfunction, and 15% with paresthesias. Eighty-five percent of patients had improvement or stabilization of neurologic symptoms with conventional radiotherapy.

Traditional treatment for spinal cord compression consists of some combination of steroids, laminectomy, and radiotherapy [6]. A number of recent studies suggest that chemotherapy alone can be as effective as the abovementioned modalities in cases of spinal cord compression caused by neuroblastoma, thus portending fewer long-term complications such as RT-associated second malignant neoplasm [11,17].

Up to 75% of mediastinal masses in children are symptomatic [18]. There are several contributing factors: 1) the smaller thoracic cage increases the chance of adjacent visceral or airway compromise, 2) the already small pulmonary reserve volume does not tolerate further reduction by lung compression or replacement, and 3) the trachea is more compliant in children and therefore more easily compressed. Symptoms include stridor, cough, dyspnea, hemoptysis, orthopnea, and life-threatening cardiovascular compromise from pericardial effusion or vena caval obstruction [12]. Upper airway problems are the result of tumors either compressing or invading the airway, especially when the masses are in the anterior superior mediastinum. Generally, the luminal cross-sectional area must be decreased to 20% of normal before symptoms become acute [2].

Information concerning the life-threatening superior mediastinal syndrome (SMS) is limited [19–22]. That syndrome differs from the superior vena cava syndrome (SVCS) in that tracheal compression is added to the SVCS signs and symptoms. The combination of signs is so often present in children that the two terms are used interchangeably [8,12]; in contrast, the SVCS is more common in adults, usually from lung cancer (65%) [6]. Non-Hodgkin's lymphoma accounts for about 70% of pediatric SMS/SVCS in other series [6,8,13], but among our patients, non-Hodgkin's lymphoma was the cause in only 25% (3 of 12). The prognosis depends on the histologic diagnosis rather than the presence of the syndrome itself. Definitive treatment depends on the underlying malignancy; for non-Hodgkin's lymphoma, radiotherapy is effective, and improvement can be seen within 12 hours [13]. Often, a situation arises in which SMS is the presenting symptom and a histologic diagnosis has not yet been established. Then a carefully directed radiation portal that excludes part of the tumor can lead to rapid relief. This technique does not compromise subsequent biopsy results, as does the use of steroids or chemotherapy if non-Hodgkin's lymphoma should be the underlying disease [13]. In our series, 10 of the 12 patients (83%) who were treated for SMS improved with radiotherapy.

The most frequent presentation of solid tumors in children is a palpable abdominal mass [18]. Wilms tumor and neuroblastoma are the most common of these. Among the 8 patients requiring abdominal treatment in our series, 5 had neuroblastoma and 2 had Wilms tumor. The eighth had acute lymphocytic leukemia and renal difficulties.

Acute neurologic compromise may be the result of a direct tumor effect, or it may be secondary to dysfunction in another organ system or to treatment. Primary dysfunction may result from either a diffuse derangement of cortical function or from damage to the centrally located ascending reticular activating system (RAS), located in the lower diencephalon and upper brain stem [23]. RAS injury is usually caused by diffusely increased intracranial pressure or by a localized cortical mass. The overall outcome of this group of patients in our series with RAS injury was 63%.

Skeletal malignancies are most commonly caused by neuroblastoma, Ewing's sarcoma, osteogenic sarcoma, and leukemia [6]. Patients with these entities commonly present with pain. Our 15 patients with pain had an excellent response (93%) following urgent irradiation.

CONCLUSION

Referrals for urgent or emergent radiation therapy are not uncommon in pediatric oncology, accounting for 12% of the children seen by us in consultation during the 6-year period reviewed. Our experience indicates that radiation therapy can be an important component of multimodal therapy in pressing situations, when rapid relief is needed, and the possible efficacy of other methods cannot be awaited. Stabilization or improvement was achieved with 80% of the 91 episodes using multimodality therapy including radiation, which were especially useful for pain caused by spinal cord compression and bone metastases.

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